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Systemic corticosteroids for the treatment of asthma exacerbations during and outside of pregnancy in an acute-care setting

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Summary
Background: Asthma exacerbations are common during pregnancy with a prevalence as high as 51.9% among women with severe asthma.
Objective: To compare the treatment of asthma exacerbations in an acute-care setting during and outside of pregnancy.
Methods: We formed a cohort of women who sought medical care for an asthma exacerbation at a teaching hospital during or in the year preceding pregnancy, between 1998 and 2008. An exacerbation was composed of one or more medical encounters in an acute-care setting (hospital-based outpatient clinic, emergency department, or during hospitalization). Data were retrieved from medical charts and health administrative databases. We compared the use of

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systemic corticosteroids (SCSs) during and outside of pregnancy with a Cox proportional hazards model.
Results: The cohort was formed of 39 women who had 40 exacerbations during and 39 exacerbations outside of pregnancy. Use of SCSs to treat exacerbations was less frequent (adjusted hazard ratio: 0.51; 95% CI: 0.31—0.84) during pregnancy. Moreover, upon the first medical encounter related to the exacerbation, SCSs, when administered, were given less frequently to women when pregnant than when non-pregnant (83% vs. 100%). The SCS prescription was filled at the community pharmacy 65% and 67% of the time when it was prescribed at discharge to women when pregnant than when non-pregnant, respectively.
Conclusion: We observed a reduced and delayed use of SCSs for the treatment of asthma exacerbations in women when pregnant than when non-pregnant, with similar numbers of women in both conditions filling their SCSs prescription in pharmacies.

Introduction

Asthma is one of the most common potentially serious medical conditions encountered during pregnancy affecting 3.7—8.4% of pregnancies [1,2]. Asthma exacerbations are common during pregnancy, with 12.6%, 25.7%, and 51.9% of women with mild, moderate, or severe asthma experiencing an exacerbation, respectively [3]. Current asthma guidelines recommend equivalent treatment of exacerbations for pregnant and non-pregnant women [4,5]. The guidelines emphasize the safety of asthma medications compared to the risk of poorly controlled asthma for the fetus, since uncontrolled asthma during pregnancy was found to be associated with increased risks of perinatal complications [4—10]. These notions were already present in the National Asthma Education and Prevention Program guidelines of 1997 [11]. Despite these recommendations, two American studies reported that the percentage of systemic-corticosteroid (SCS) use for the treatment of an asthma exacerbation was about 20% less at the emergency department (ED) and at discharge between pregnant and non-pregnant women [12,13]. These studies did not evaluate medical visits at a hospital-based outpatient clinic, or hospitalizations.

The main purpose of this study was to compare SCS use for the treatment of asthma exacerbations during and outside of pregnancy in a non-US acute-care setting, including medical visits at a hospital-based outpatient clinic, ED visit, and/or hospitalization. The study was undertaken because the literature reports that prescribing ED practices to treat asthma exacerbations differ between US and non-US centers [14].

Methods

Study design

From a cohort of pregnant asthmatic women giving birth in the province of Quebec, Canada, between 1998 and 2008 we identified women who had an asthma exacerbation managed at the Centre hospitalier universitaire de Sherbrooke (CHUS),—a teaching hospital—during or in the year preceding pregnancy [15]. The inclusion criteria for this cohort were: (1) singleton delivery between 1998 and 2008, (2) a medical encounter (medical visit at a hospital-based outpatient clinic, ED visit, and/or hospitalization) for an asthma exacerbation at the CHUS one year prior to or during pregnancy, (3) 45 years of age or younger at the time of delivery, (4) having at least one diagnosis of asthma (International Classification of Diseases [ICD], ICD-9 code: 493 [except 493.2] or ICD-10 code: J45) and at least 1 prescription for an asthma medication filled in the year before or during pregnancy, and (5) being covered by the RAMQ drug-insurance plan for at least one year before the exacerbation and to the end of pregnancy. If a woman contributed several pregnancies, we kept only the two most recent. Information on in- and outpatient care provided in the province of Quebec was obtained from two administrative databases: the *Régie de l'assurance-maladie du Québec* (RAMQ) (providing information on medication prescriptions (i.e. SCSs) filled in community pharmacies, outpatient medical visits, and ED visits) and MED-ECHO (providing information on asthma-related hospitalizations). To determine pregnancy duration, we retrospectively identified the date of the first day of the subject's last menstrual period and the date of delivery for each pregnancy using gestational age at birth and offspring date of birth.

Asthma exacerbations and hospital data collection

An asthma exacerbation was defined as one or more medical encounters related to the condition when no more than 14 days elapsed between two adjacent visits. A medical encounter was considered to be due to an asthma exacerbation when one of the following terms was found in the medical chart: bronchospasm, asthma exacerbation, asthma crisis, status asthmaticus, or decompensated asthma. Two persons (MC and CR) independently assessed whether or not each medical encounter was due to an asthma exacerbation. All medical encounters were reviewed whether or not an ICD-9 code for asthma was present. Discordant cases were resolved by a consensus review by two pharmacists (BC and MFB). For each medical encounter due to an asthma exacerbation, we collected the visit's starting and ending dates as well as its location (hospital-based outpatient clinic, ED, and/or hospitalization) from the hospital electronic health

record. If a woman was seen in different locations during the exacerbation, a single location was attributed according to the following hierarchy: hospitalization, ED visit, and hospital-based outpatient visit. The exacerbation's duration was defined as the last day of the last medical encounter minus the first day of the first medical encounter +1, including days between medical encounters. To illustrate, for a patient seen at the ED on days 1 and 2, sent home on day 2, and then seen again at the ED on days 5 and 6, the duration of exacerbation would be 6 days. Data on spirometry and asthma medications taken during medical encounters and prescribed at discharge were collected by a single individual (MC) using a standardized electronic-data form.

Outcomes

The use of SCSs during an exacerbation or in the subsequent 14 days was the main outcome. Exposure to SCSs (prednisone or methylprednisolone) during a medical encounter was defined as an active prescription of SCSs in the patient's chart. Outpatient exposure to SCSs (prednisone) was defined as at least one prescription filled at a community pharmacy, from the start of the exacerbation and up to 14 days subsequent to the exacerbation. More specifically, for the Cox regression, the outcome was defined as the time to the first SCS exposure (medical encounter or community pharmacy). The secondary outcomes were: (1) the use of SCSs upon the first medical encounter for an exacerbation, (2) the occurrence of a second medical encounter during an exacerbation, and (3) the use of SCSs upon a second medical encounter.

Potential confounding variables

Potential confounding variables measured at the time of the exacerbation included maternal age (18–34 years, other), maternal receipt of social assistance and the severity of the exacerbation estimated by the maximal daily dose of short-acting B_2-agonists (SABA) administered during a medical encounter (0–1200 μg, >1200 μg). Potential confounding variables measured in the year preceding the exacerbation included diabetes (including gestational), hypertension (including pregnancy-induced hypertension) and asthma control measured by a validated algorithm (based on the use of SABA and SCSs and on the occurrence of hospitalizations or ED visits for asthma) [16]. The SABA dose used during the medical encounters was retrieved from the medical charts; all other confounding variables were retrieved from the administrative databases. A detailed description of the asthma control algorithm is available upon request. Forced expiratory volume in one second (FEV_1) values were reported as a descriptive variable but was not included in the multivariate models because of missing values. FEV_1 were shown to be valid indicators of asthma control in pregnancy [17].

Statistical analysis

Descriptive statistics were used to compare the exacerbation's characteristics and SCS use between exacerbations occurring during and outside pregnancy. We produced Kaplan–Meier curves to illustrate crude hazard functions. We estimated the crude and adjusted hazard ratios (HRs) for SCS use by comparing exacerbations occurring during and outside of pregnancy with a marginal Cox model for clustered data (a woman could contribute more than one exacerbation and be included in the pregnant and non-pregnant groups) with a robust sandwich covariance estimate to account for the intracluster correlation [18]. A descriptive analysis of the proportion of SCS use upon the first medical encounter, the need for a second medical encounter for an ongoing exacerbation, and SCS use upon the second medical encounter was also performed to compare the exacerbations of women when pregnant and when non-pregnant. Statistical analyses were performed using SAS version 9.2 (SAS Institute, Inc., Cary, NC).

Ethics approval

We obtained approval from the Commission d'accès à l'information du Québec (Quebec access-to-information commission) prior to requesting and linking the information from the Med-Echo and RAMQ databases to data from the women's charts. This study was approved by the ethics committees of the *Hôpital du Sacré-Coeur de Montréal* and the *Centre hospitalier universitaire de Sherbrooke*.

Results

Exacerbation's characteristics

As shown in Fig. 1, the cohort was composed of 39 women who had 79 exacerbations: 40 during and 39 outside of pregnancy. Of the 40 exacerbations during pregnancy, 8, 17, and 15 occurred in the first, second, and third trimesters respectively. Table 1 gives the characteristics of the exacerbations according to whether or not they occurred during pregnancy. The women had a mean age of 25.3 years and 60.8% were receiving social assistance at the time of the exacerbation. The mean number of medical encounters per exacerbation was 1.2 during and 1.1 outside of pregnancy. Fig. 1 describes the different locations of the medical encounters accounting for the exacerbations. The similar forced expiratory volume in one second (FEV_1) values suggest a comparable severity of the exacerbations between the groups, but the data were available for 21 exacerbations that occurred during and 24 that occurred outside of pregnancy. Twenty-eight percent of the exacerbations were managed during hospital-based outpatient-clinic visits with higher FEV_1 values (data not shown) during these visits compared to ED visits or hospitalizations. This might indicate less severe exacerbations in the hospital-based outpatient-clinic setting. The high frequency of weekly SABA use and the number of SCS prescriptions in the year preceding the exacerbations suggest that asthma control was poor in both groups. The mean daily dose of ICS was similar in both groups and could be qualified as a low dose according to GINA guidelines [4]. long-acting β_2-agonists (LABA) use was greater outside of pregnancy, which was expected for a class of medication with limited safety data during pregnancy [15]. The pregnant group comprised a larger proportion of women with diabetes.

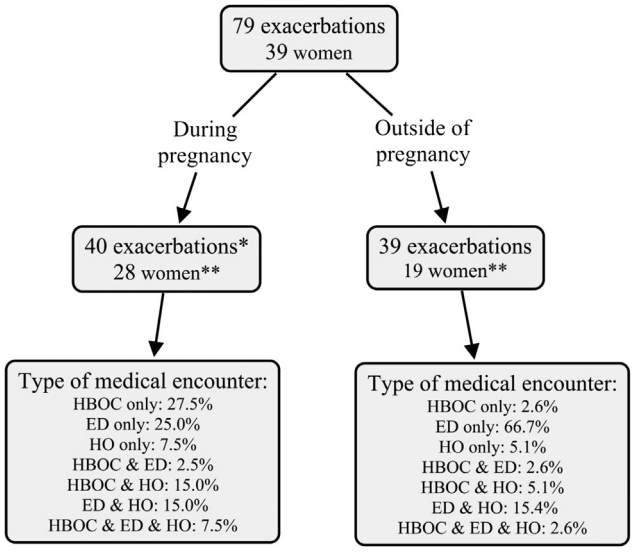

Figure 1 Distribution of the exacerbations during and outside of pregnancy. ED, emergency department; HBOC, hospital-based outpatient clinic; HO, hospitalization. *A total of 40 exacerbations occurred during 30 different pregnancies: 24 women had only one exacerbation, 4 women had two exacerbations, and 2 women had four exacerbations. **Eight women had exacerbations during and outside of pregnancy.

Table 1 Characteristics of the exacerbations that occurred during and outside of pregnancy.

Subjects *n*	Exacerbations during pregnancy	Exacerbations outside of pregnancy
	40	39
Characteristics at the time of the exacerbation		
Age, mean ± SD	26.3 ± 5.3	24.2 ± 5.5
Receipt of social assistance, *n* (%)	24 (60.0)	24 (61.5)
Location of medical encounter during the exacerbation, n (%)		
Hospital-based outpatient clinic	11 (27.5)	1 (2.6)
Emergency room	11 (27.5)	27 (69.2)
Hospitalization	18 (45.0)	11 (28.2)
Duration of exacerbation		
1 day	12 (30.0)	19 (48.7)
Median (min.—max.)	3.0 (1—36)	2.0 (1—20)
FEV_1[a],% predicted ± SD	59.2 ± 19.2	55.8 ± 15.3
Use of SABA, n (%)		
0—1200 μg[b]	22 (55.0)	20 (51.3)
>1200 μg	18 (45.0)	19 (48.7)
Characteristics in the year preceding the exacerbation		
Asthma control, *n* (%)	14 (35.0)	6 (15.4)
ICS non-users, *n* (%)	10 (25.0%)	12 (30.8%)
ICS dose[c] among users	231.8 ± 215.8	257.9 ± 157.7
Use of LABA, *n* (%)	11 (27.5)	16 (41.0)
SABA (doses/week), n (%)		
0—3	17 (42.5)	7 (18.0)
4—10	6 (15.0)	5 (12.8)
>10	17 (42.5)	27 (69.2)
SCSs,# prescriptions, mean ± SD	2.5 ± 3.1	2.9 ± 3.0
Hypertension[d], *n* (%)	5 (12.5)	4 (10.3)
Diabetes[e], *n* (%)	8 (20.0)	2 (5.1)

FEV_1, forced expiratory volume; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; SABA, short-acting beta-agonist; SCS, systemic corticosteroids; SD, standard deviation.
[a] FEV_1 values were available for 21 and 24 exacerbations in pregnant and non-pregnant women, respectively.
[b] Includes use of patient's own medication without information on the dose.
[c] Average dose/day in fluticasone-equivalent.
[d] Includes pregnancy-induced hypertension.
[e] Includes gestational diabetes.

Systemic corticosteroids use

SCS use (presented in Table 2 and Fig. 2) was lower when the exacerbation occurred during pregnancy. There was a greater use of SCS in the first compared to the second and third trimesters. A secondary analysis revealed that use of SCSs was lower in pregnant compared to non-pregnant women regardless of the location of the medical encounter: hospital-based outpatient clinic visits (72.7% vs. 100%), ED visits (63.6 vs. 77.8%) and hospitalizations (77.8% vs. 90.9%). An SCS prescription was filled at the community pharmacy (during or outside of pregnancy) in 44 of the 79 exacerbations. In all but one of these 44 exacerbations, the prescription was filled in the seven days following the last medical encounter for an exacerbation. A discharge SCS prescription was documented in the patient's chart in 47 of 79 exacerbations. Similar percentages of women, when pregnant (13/20, 65.0%) and non-pregnant (18/27, 66.7%) filled their SCSs prescription at a community pharmacy (up to 14 days subsequent to the exacerbation) when a discharge prescription for an SCS was documented in the patient's chart.

Multivariate model

The adjusted model presented in Table 3 revealed that SCSs were significantly used less during pregnancy, with an adjusted hazard ratio of 0.51 (95% CI: 0.31—0.84). This model also revealed that women with diabetes and those who had doses of SABA >1200 μg during a medical encounter were significantly more likely to use SCSs. Age and a diagnosis of hypertension in the year preceding the exacerbation were not included in the final Cox model because these factors did not meet the proportional hazards assumption and because the small sample size precluded stratification according to these variables.

Timing of systemic corticosteroids use

Fig. 3 shows that all women who used SCSs for an exacerbation that occurred outside of pregnancy received it during the first medical encounter (including the subsequent 14 days), while the corresponding figure was 82.8% during pregnancy. During pregnancy, when SCSs were not used during the first medical encounter, the mean delay

Table 2 Use of systemic corticosteroids in exacerbations that occurred during and outside of pregnancy.

Subjects, *n*	Exacerbations during pregnancy	Exacerbations outside of pregnancy
	40	39
Systemic corticosteroids use, *n* (%)	29 (72.5)	32 (82.1)
During medical encounter and filled in a community pharmacy	12 (30.0)	17 (43.6)
During medical encounter only	9 (22.5)	8 (20.5)
Filled in community pharmacy only	8 (20.0)	7 (18.0)
None	11 (27.5)	7 (18.0)
Systemic corticosteroids use[a], *n* (%)		
First trimester	7 (87.5)	—
Second trimester	12 (70.6)	—
Third trimester	10 (66.7)	—

[a] Systemic corticosteroid use during a medical encounter or filled in community pharmacy.

Table 3 Crude and adjusted hazard ratios of the use of systemic corticosteroids during and outside of pregnancy.

	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
Exacerbation occurring during vs. outside of pregnancy	0.60 (0.39—0.94)	0.44 (0.23—0.85)
Receipt of social assistance at the time of the exacerbation (yes vs. no)	0.78 (0.54—1.13)	0.74 (0.48—1.12)
Use of SABA during a medical encounter		
0 μg—1200 μg[a]	Reference	Reference
>1200 μg	2.18 (1.52—3.14)	2.37 (1.55—3.63)
Location of medical encounter during the exacerbation, *n* (%)		
Hospital-based outpatient clinic	Reference	Reference
Emergency room	1.25 (0.71—2.18)	0.86 (0.46—1.63)
Hospitalization	1.48 (0.86—2.56)	0.67 (0.35—1.27)
In the year preceding the exacerbation		
Uncontrolled asthma	1.26 (0.76—2.10)	1.13 (0.62—2.04)
Diabetes	1.58 (0.99—2.54)	2.26 (1.18—4.34)

[a] Includes use of patient's own medication without information on the dose recorded in the medical chart.

between the first day of the exacerbation and their use was 5.8 days. Although limited to few observations, Fig. 3 also shows that, in pregnancy, when an SCS was not received during the first medical encounter, a second medical encounter was necessary in 37.5% of the exacerbations vs. 12.5% when an SCS was used.

Discussion

Main findings

We observed a reduced and delayed use of SCSs for the treatment of asthma exacerbations in women when pregnant than when non-pregnant. The treatment of an exacerbation during pregnancy was more often done during hospitalization and in outpatient-clinic settings compared to outside of pregnancy, when ED visits accounted for 69% of visits.

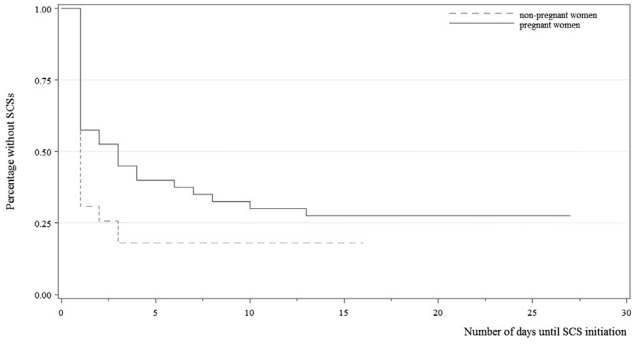

Figure 2 Kaplan—Meier curves for the use of systemic corticosteroids during and outside of pregnancy. The longer curve for the exacerbations of the pregnant women indicates a longer duration of exacerbation without systemic corticosteroids.

Strengths and limitations

Our study has some limitations. Due to the retrospective study design, we were unable to characterize the severity of the exacerbation based on symptoms. Instead, we relied on the maximum daily dose of SABA used during a medical encounter and on the first recorded FEV_1 value, the latter being available for only half of the exacerbations. The maximum daily dose of SABA cut-off was based on the clinical experience of the investigators. It is possible that pregnant women seek medical advice at an earlier, less severe, stage of an exacerbation because of concern for the baby. Other limitations are the fact that the study was conducted at a single teaching hospital and that 61% of the women were receiving social assistance, limiting the generalizability of the results. The reviewers of the patient's charts were not blinded to the presence or absence of pregnancy or the study's objectives. The study's strengths include the assessment of all medical encounters for an exacerbation. The avoidance of recall bias by assessing the use of pre-exacerbation medical resources (from any institution) as well as outpatient asthma prescriptions filled in any community pharmacy in the pre- and post-exacerbation periods via data retrieved from provincial databases is another strong point. Moreover, the social desirability bias, in which physicians and women can change their behaviors due to prospective assessment, was avoided in this non-interventional study.

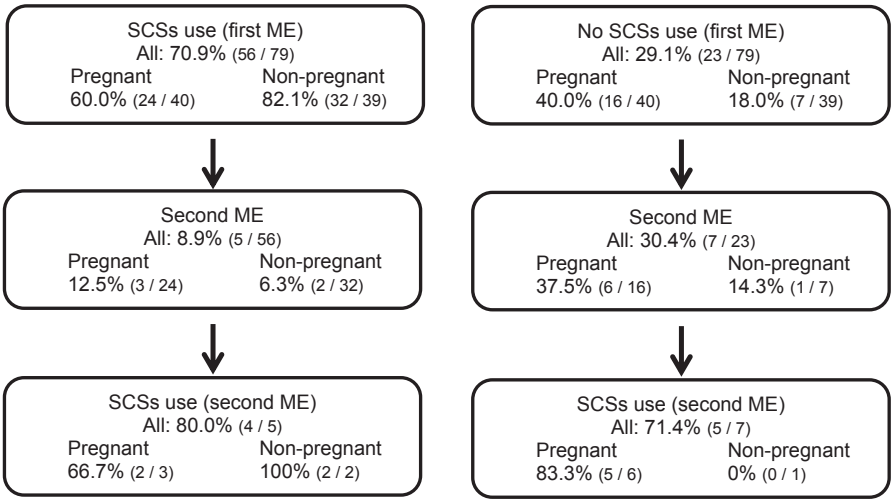

Figure 3 Systemic corticosteroid use[a] during the first and subsequent medical encounters for an exacerbation. ME, medical encounter; SCSs, systemic corticosteroids. [a]Systemic corticosteroid use during a medical encounter or prescription filled at a community pharmacy up to 14 days following the medical encounter and before the subsequent medical encounter.

Interpretation

In our study, SCS use during a medical encounter was 52.5% for women when pregnant and 64.1% for women when non-pregnant, which is comparable to what was observed in the studies carried out by Cydulka [12] (44% during and 66% outside of pregnancy) and McAllister [13] (51% during and 72% outside of pregnancy). Our study, which assessed exacerbations managed in hospital-based outpatient clinic, ED, and hospitalization setting differs from the work of Cydulka [12] and McAllister [13], who assessed exacerbations treated only in the ED. Two other important methodological differences are that we analyzed all medical encounters related to an exacerbation as well as multiple exacerbations for the same woman, while other studies were limited to a woman's first ED visit. When SCS were not used during the first but used in the second medical encounter of an exacerbation, the mean delay for SCS use was 5.8 days possibly exposing the fetus to prolonged hypoxia which could lead to poor perinatal outcomes. We believe that the predominant safety concern of the physicians when prescribing SCSs during pregnancy is the risk of cleft lip/palate. In the 2004 pregnancy specific guidelines of the National Asthma Education and Prevention Program (NAEPP), the risk for isolated cleft lip with or without cleft palate was estimated at 0.1% in the general population and at 0.3% for women exposed to oral corticosteroids in the first trimester of pregnancy [9]. In the NAEPP guidelines and in the British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) Asthma Guidelines section on pregnancy, the authors insist on the facts that the association between SCS and cleft lip/palate has not been constantly demonstrated and is partially based on studies with prolonged use of SCS and at greater doses than the usual doses to treat asthma exacerbations [5,9]. A summary of the studies on the safety of SCSs use during pregnancy is provided in the NAEPP 2004 guidelines [19]. In the pregnancy section of the GINA [4] and BTS/SIGN guidelines [5] and in the NAEPP 2004 [9] pregnancy guidelines, the authors mention the importance of SCSs for the treatment of asthma exacerbations during pregnancy without providing any efficacy data during or outside pregnancy, the focus being on the safety of SCSs. We assume that the recommendations made in the guidelines of the efficacy of SCSs for the treatment of exacerbations during pregnancy is based on data outside of pregnancy. The greater proportion of medical encounters in hospital-based outpatient clinic and higher FEV_1 values could be an indication of less severe exacerbations in pregnant women and explain part of the difference in SCSs use. The fact that the vast majority of these visits were in obstetrics clinics points to the alternative hypothesis of a different pattern of access to care during pregnancy. It is also possible that the higher hospitalization rate seen in pregnant women is done to assure a better follow-up and is not indicative of more severe exacerbations. We also found that an SCS prescription was filled at a community pharmacy up to 14 days subsequent to the exacerbation in 50.0% and 61.6% of the exacerbations for women when pregnant and when non-pregnant, respectively. Other researchers found an SCS prescription upon discharge from the ED in 38%—41% and 64%—69% of exacerbations of pregnant and non-pregnant women, respectively [12,13]. The fact that 66.0% of SCSs prescribed at discharge in our study were actually filled at a community pharmacy allows for a better estimate of true outpatient treatment following a medical encounter. With similar percentages of prescribed SCSs being filled in community pharmacies for women when pregnant and when non-pregnant, we can conclude that the observed differences in SCS use are due to prescribing differences for pregnant and non-pregnant women. Differences in the percentages of pregnant and non-pregnant women filling their SCSs prescriptions could have been expected in light of the "steroid phobia" described in a recent analysis of the concerns of pregnant women with asthma, although it was not observed in our study [20].

Conclusion

We observed a reduced and delayed use of SCSs for the treatment of asthma exacerbations during pregnancy as compared to outside of pregnancy in a Canadian teaching hospital of similar magnitude to that observed previously in the United States [12,13]. These exacerbations occurred among women who were using low daily doses of ICS, high weekly doses of SABA, and more than two courses of SCSs in the previous year, indicating suboptimal asthma management. These observations do not reflect the recommendations of current asthma treatment guidelines, which emphasize the importance and safety of the use of adequate controller medications, including the use of moderate to high doses of ICSs during pregnancy when required, compared to the risk to the fetus due to of poorly controlled asthma [4,9,10]. The next research step is to assess the impact of this reduced and delayed use of SCSs on pregnancy outcomes.

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Author contributions

Contributors: LB, BC, MFB, and AF conceived and designed the study and contributed to data analysis. LB and BC wrote the manuscript. LB acquired the funding. BC, MFB, AF, CL, PL, ER, MC, CR, LB interpreted the data, revised the manuscript, had access to complete study data, and had authority over manuscript preparation as well as approval of the final version and the decision to submit for publication.

Disclosure of interests

BC had financial support from the Canadian Institutes of Health, Iris-Québec, and Fonds recherche du Québec en santé and grants from Sanofi, Eli Lilly, Novartis, and Novo-Nordisk as well as fee for lectures from Eli Lilly. CL received: honoraria from GlaxoSmithLine for consultancy work and for lectures, including speaker bureau services from AstraZeneca and Merck; grants from AllerGen and Aerocrine; royalties from UpToDate and payment for the development of educational presentations from AstraZeneca. LB had financial support from the Canadian Institutes of Health and Iris-Québec and grants and personal fees from AstraZeneca, Pfizer and Genentech, grants from Novartis, Merck and Sanofi. MFB co-holds the AstraZeneca Pharmaceutical Endowment Chair in Respiratory Health and has received a research grant from GSK to conduct an investigator-initiated project. PL has received payment for delivering educational presentations for GlaxoSmithKline, AstraZeneca, Boehringer Ingelheim, Merck, and Novartis. AF, ER, CR and MC report no competing interests.

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